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(54) Title: NOVEL FORMS OF 2,3-DIMETHYL-8-(2-ETHYL-6-METHYLBENZYLAMINO)-IMIDAZO (1,2-A)PYRIDINE-6-CARBOXAMIDE

(57) Abstract: The present invention relates to novel crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt. Further, the present invention also relates to use of said compounds for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them and processes for obtaining them.

Novel forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo (1,2-a)pyridine-6-carboxamide

Field of the invention

The present invention relates to novel crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt. Further, the present invention also relates to use of said compounds for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them and processes for obtaining them.

Background of the invention and prior art

In the formulation of drug compositions, it is important for the active pharmaceutical ingredient (API) to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations (e.g. oral dosage forms such as tablets) comprising the active pharmaceutical ingredient.

Further, in the manufacture of oral drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of the active pharmaceutical ingredient is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active pharmaceutical ingredient are also very important factors. The active pharmaceutical ingredient, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active pharmaceutical ingredient, e.g. its chemical composition, density, hygroscopicity and solubility.

Amorphous materials may present problems in this regard. For example, such materials are typically more difficult to handle and to formulate, provide for unreliable dissolution, and are often found to be more unstable.

Thus, in the manufacture of commercially viable and pharmaceutically acceptable drug compositions, it is important, wherever possible, to provide the active pharmaceutical ingredient in a substantially crystalline and stable form.

International patent applications WO 99/55705 and WO 99/55706 disclose a number of compounds, referred to as imidazo pyridine derivatives, which are reversible acid pump inhibitors.

WO 99/55706 discloses the compound 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. A process for the synthesis of this compound is described in Example 1.4 of WO 99/55706.

WO 99/55705 discloses the compound 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt is used as the starting material in Example 2.5 to produce the corresponding carboxylic acid by alkaline hydrolysis.

WO 99/55705 contains no information about the solid state properties of the mesylate salt compounds. WO 99/55705 does further not disclose how the different crystal forms of the mesylate salt compounds may be obtained and does not predict the properties of such crystal forms.

Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A.

Figure 2 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A´.

Description of the invention

It has surprisingly been found that 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo-[1,2-a]pyridine-6-carboxamide mesylate salt can exist in more than one crystal form. The

compounds are hereinafter referred to as 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt forms A and A´.

It is thus an object of the present invention to provide crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt with advantageous properties.

It is an aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities;

Form A		**Form A**		**Form A**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
14.3	vs	4.78	w	3.54	w
8.4	m	4.45	w	3.39	w
7.7	m	4.34	w	3.30	w
7.23	w	4.28	w	3.13	w
7.16	s	4.19	w	3.06	w
6.8	w	4.15	w	2.95	w
6.2	w	4.06	w	2.87	w
5.9	w	4.02	w	2.80	w
5.4	m	3.87	w	2.39	w
5.1	w	3.79	w	2.30	w
4.94	w	3.70	w	2.05	w
4.83	w	3.58	w		

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A. The relative

intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity*	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)

* The relative intensities are derived from diffractograms measured with variable slits.

The definition above has also been used when identifying the peaks of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A', *vide infra.*

Differential Scanning Calorimetry (DSC) on form A showed a single melting endotherm with extrapolated onset of ca 300°C (ca 135 J/g). TGA showed that decomposition starts at ca 250°C and that there is no weight loss up to this temperature.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A'.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A', according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 2, exhibiting substantially the following d-values and intensities;

Form A´		Form A´		Form A´	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
14.1	vs	4.34	s	3.35	m
8.4	s	4.26	m	3.28	vs
8.2	m	4.14	s	3.13	m
7.7	vs	4.04	s	3.11	m
7.3	s	4.00	s	3.06	w
7.1	s	3.94	m	2.94	w
6.7	s	3.85	s	2.84	m
6.2	m	3.81	m	2.73	m
5.9	vs	3.76	s	2.68	m
5.4	vs	3.68	s	2.60	m
5.1	m	3.65	m	2.54	m
5.0	s	3.56	m	2.40	w
4.92	m	3.52	s	2.37	w
4.79	s	3.48	m	2.29	m
4.43	s	3.45	m	2.13	w
4.40	m	3.39	m		

Differential Scanning Calorimetry (DSC) on form A´ showed a single melting endotherm with extrapolated onset of ca 297°C (ca 131 J/g).

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A´ is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is possible to crystallize 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salts, i.e. the compounds of the present invention, in one single solvent or in a mixture of solvents. However, we prefer that the crystallization is from one single solvent.

Crystallization of compounds of the present invention from an appropriate solvent system, containing at least one solvent, may be achieved by attaining supersaturation in a solvent

system by solvent evaporation, by temperature decrease, and/or via the addition of anti-solvent (i.e. a solvent in which the compounds of the invention are poorly soluble).

Crystallization may also be initiated and/or effected with or without seeding with crystals of the appropriate crystalline compound of the invention.

Crystallization of compounds of the present invention can be achieved starting from pure 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt of any form, or mixtures of any form.

Whether an anhydrate or a solvate crystallizes is related to the kinetics and equilibrium conditions of the respective forms at the specific conditions. Thus, as may be appreciated by the skilled person, the crystalline form that is obtained depends upon both the kinetics and the thermodynamics of the crystallization process. Under certain thermodynamic conditions (e.g. solvent system, temperature, pressure and concentration of compound of the invention), one crystalline form may be more stable than another (or indeed any other). However, crystalline forms that have a relatively low thermodynamic stability may be kinetically favored. Thus, in addition, kinetic factors, such as time, impurity profile, agitation, the presence or absence of seeds, etc. may also influence which form that crystallizes.

According to the invention there is further provided a process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt forms A and A´.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A is obtained upon crystallization from ethanol.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A´ is obtained upon crystallization from acetonitrile in the presence of methanol.

The preparation and characterization of different forms of compounds of the invention are described hereinafter. Different crystalline forms of the compounds of the invention may

be readily characterized using e.g. X-ray powder diffraction (XRPD) methods or Raman spectroscopy.

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallization is preferably carried out by seeding with seed crystals of the desired crystalline form. This applies particularly to each of the specific crystalline forms which are described in the Examples.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt forms A and A´ obtained according to the present invention are substantially free from other crystal and non-crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt. The term "substantially free from other crystal and non-crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt" shall be understood to mean that the desired crystal form of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt contains less than 50%, preferably less than 10%, and more preferable less than 5% of any other forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt.

In accordance with the invention, the compounds of the invention may be administered and used as described in WO 99/55705 and WO 99/55706, the content of which is hereby incorporated by reference.

The compounds of the invention may be further processed before formulation into a suitable pharmaceutical formulation. For example, the crystalline form may be milled or ground into smaller particles.

According to a further aspect of the invention, there is provided a pharmaceutical formulation including a compound of the invention in admixture with at least one pharmaceutically acceptable adjuvant, diluent or carrier.

According to a further aspect of the invention there is provided a method of treatment of a condition where inhibition of gastric acid secretion is required or desired, which method

includes administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment.

For the avoidance of doubt, by "treatment" we include the therapeutic treatment, as well as the prophylaxis, of a condition.

The compounds of the invention have the advantage that they are in a form that provides for improved ease of handling. Further, the compounds of the invention have the advantage that they may be produced in forms that have improved chemical and solid state stability as well as lower hygroscopicity. Thus, the compounds may be stable when stored over prolonged periods.

The invention is illustrated, but in no way limited, by the following examples.

Examples

General Procedures

X-ray powder diffraction (XRPD) analysis was performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. et al (1995), Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD.

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 instrument, according to standard methods, for example those described in Höhne, G. W. H. et al (1996), Differential Scanning Calorimetry, Springer, Berlin.

Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA850 instrument.

DSC onset temperatures may vary in the range ±5°C (e.g. ±2°C), and XRPD distance values may vary in the range ±2 on the last decimal place. It should be understood that the d-values of X-ray powder diffraction pattern exhibits variation depending on e.g. equipment used, sample preparation, and operator. However the precision and repeatability of said technique is found to be high and thus X-ray powder diffraction pattern exhibiting substantially the same d-values should be obtained if repeated.

Example 1

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

10 g (0.0331 mol) of 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide hydrobromide was suspended in isopropanol (50 ml). 1.01 g (0.00674 mol, 0.2 eq.) of NaI and 11.46 g (0.0829 mol, 2.5 eq.) of K_2CO_3 were added. The suspension was heated to 81°C inner temperature. A solution of 7.72 g (0.0458 mol, 1.38 eq.) 2-ethyl-6-methylbenzylchloride diluted in isopropanol (50 ml) was added over 6 h. Stirring was continued for 1 h at 81°C. 80% of the solvent wasdistilled off (rotary evaporator, 45°C, 80 mbar). The suspension was cooled to 20°C over 2 h. The solid was filtered off .

The material was suspended in water (100 ml) and stirred for 3 h at 40°C. The solid was filtered off and washed with water (2 x 50 ml). The material was dried on the rotary evaporator (45-50°C, 20-1 mbar, 18 h) to give 9.49 g.
Yield: 84.8%

Example 2

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A

12.35 g (0.0367 mol) of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was suspended in n-butanol (120 ml). The mixture was heated to 80-83°C (solution). Methanesulfonic acid (3.05 g, 0.0317 mol, 1.1 eq.) was added over 10 min. Precipitation started immediately. Heating was continued for 40-50 min, the suspension was cooled to 20°C over 3 h. The suspension was filtered off and washed with butanol (25 ml). The solid was suspended in ethanol (100 ml) and heated to reflux for

30 min, cooled to 20°C over 2 h, stirred an additional hour at 20°C, filtered off and washed with ethanol (2x30 ml) to obtain 11.61 g of a white solid (0.0268 mol).
Yield: 93%

Example 3

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A′.

50 mg of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt was added to 40 ml acetonitrile with *ca* 0.24 ml methanol in a beaker covered with plastic film. The suspension was left to stir for two months. When the volume had decreased to *ca* 5 ml, the plastic film was removed and the sample evaporated to dryness in one day. The sample was analyzed with pXRD, DSC, and HPLC.

CLAIMS

1. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt being in a substantially crystalline form.

2. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form A		**Form A**		**Form A**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
14.3	vs	4.78	w	3.54	w
8.4	m	4.45	w	3.39	w
7.7	m	4.34	w	3.30	w
7.23	w	4.28	w	3.13	w
7.16	s	4.19	w	3.06	w
6.8	w	4.15	w	2.95	w
6.2	w	4.06	w	2.87	w
5.9	w	4.02	w	2.80	w
5.4	m	3.87	w	2.39	w
5.1	w	3.79	w	2.30	w
4.94	w	3.70	w	2.05	w
4.83	w	3.58	w		

3. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A´ according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form A´		**Form A´**		**Form A´**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
14.1	vs	4.34	s	3.35	m
8.4	s	4.26	m	3.28	vs
8.2	m	4.14	s	3.13	m
7.7	vs	4.04	s	3.11	m
7.3	s	4.00	s	3.06	w
7.1	s	3.94	m	2.94	w
6.7	s	3.85	s	2.84	m
6.2	m	3.81	m	2.73	m
5.9	vs	3.76	s	2.68	m
5.4	vs	3.68	s	2.60	m
5.1	m	3.65	m	2.54	m
5.0	s	3.56	m	2.40	w
4.92	m	3.52	s	2.37	w
4.79	s	3.48	m	2.29	m
4.43	s	3.45	m	2.13	w
4.40	m	3.39	m		

4. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A as defined in claim 2 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt of any form, or a mixture of any form in etanol,

b) allowing the solution or suspension to crystallize, and

c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A thus obtained.

5. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A´ as defined in claim 3 comprising the steps of:
a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt of any form, or a mixture of any form in acetonitrile containing some methanol,
b) allowing the solution or suspension to crystallize, and
c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt form A´ thus obtained.

6. A process according to claims 4 or 5, characterized in that seeds are added to the solution/suspension to induce crystallization.

7. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt prepared according to any of claims 3 to 6.

8. The use of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate salt as defined in claims 1 to 3 in therapy.

9. A pharmaceutical formulation comprising 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide as defined in claims 1 to 3 in admixture with at least one pharmaceutically acceptable excipient.

10. The use of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate as defined in claims 1 to 3, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

11. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate as defined in claims 1 to 3, to a patient suffering from gastrointestinal disorders.

Figure 1. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate form A measured with variable slits.

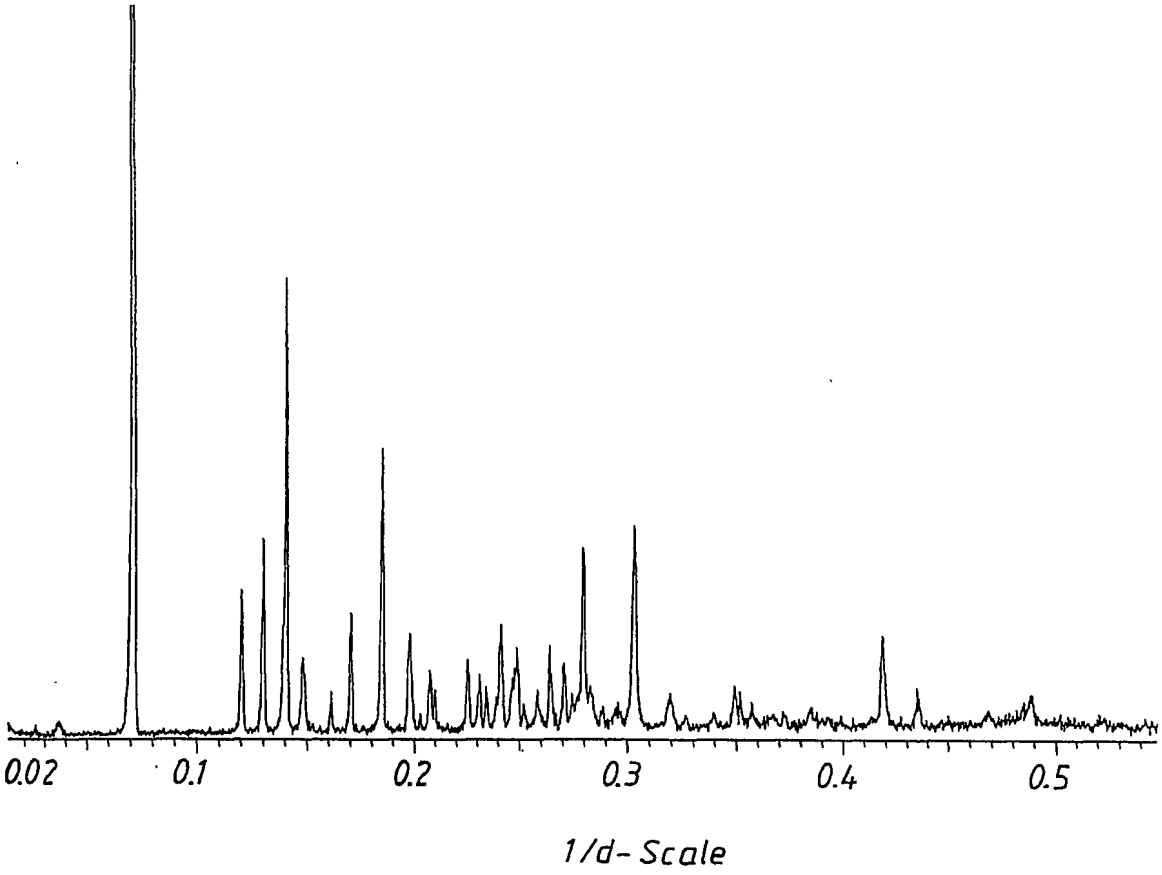
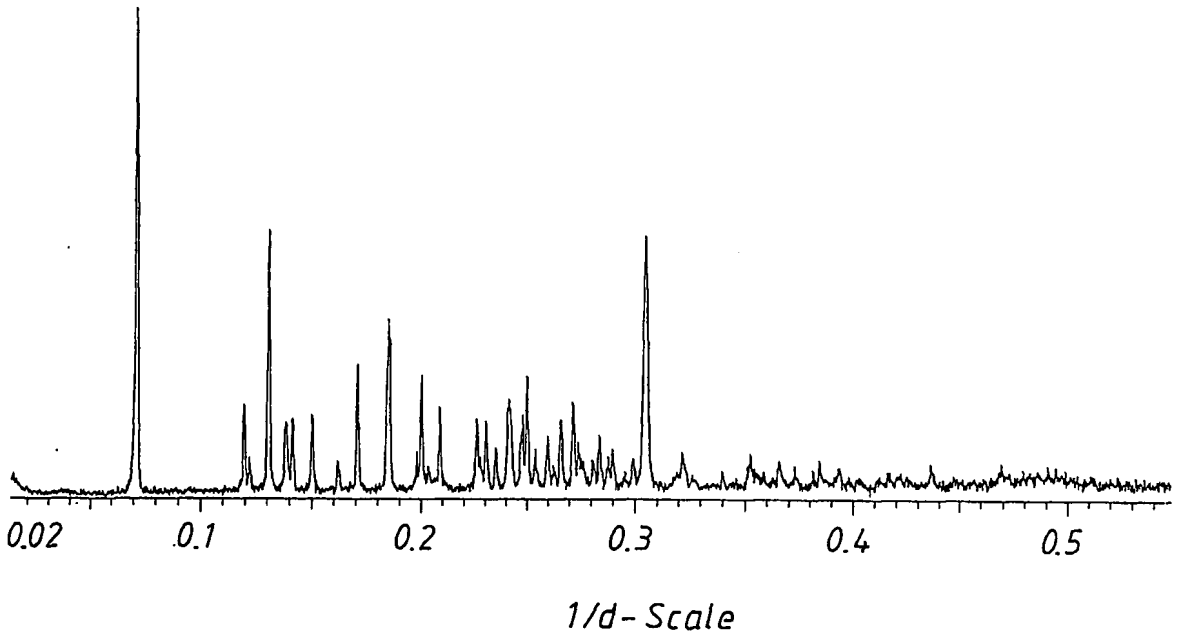


Figure 2. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate form A′ measured with variable slits.



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/4188, A61K 31/437, C07D 471/04, A61P 1/00
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9955705 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 36, example 2.5; abstract; claim ---	1-7
X	WO 9955706 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 24, example 1.4; abstract; claim --- --------	1-11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2002	14 -05- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Per Renström/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00163

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8, 11
because they relate to subject matter not required to be searched by this Authority, namely:

see

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00163

Box I.1

Claim 8 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

Claim 11

See PCT Rule 39.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.
PCT/SE 02/00163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 6313137 B	06/11/01
		WO 9955706 A	04/11/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.
PCT/SE 02/00163

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